Severe late complications after radiotherapy for advanced cervical cancer with special emphasis on brachytherapy

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Table of contents

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Abbreviations

2D	2 dimensional
3D	3 dimensional
AP-PA	anterior-posterior/posterior-anterior
BED	Biological equivalent dose
CLE	Consequential late effects
CT	Computer tomography
CTV	Clinical Target Volume
CV	Coefficient of Variance
D_{max}	Clinically relevant maximum dose
D_x	Dose to x % of a target volume
D_{ycc}	The minimum dose in the y cm^3 most irradiated volume
DR	Direct reconstruction
DVH	Dose-volume histogram
EORTC	European Organization for the Research and Treatment of Cancer
EBRT	External beam radiotherapy
EQD_2	Equivalent dose in 2Gy fractions
FIGO	International Federation of Gynecology and Obstetrics
GEC-ESTRO	Groupe Européen Curiethérapie-European Society for Therapeutic Radiology and Onclogy
gEUD	generalised equivalent uniform dose
GI	Gastrointestinal
GTV	Gross Tumour Volume
GU	Genitourinary
HDR	High dose rate
ICBT	Intracavitary brachytherapy
ICRU	International Commission on Radiation and Measurements
LDR	Low dose rate
LENT	Late effects normal tissue
LIB	Library plan
LKB model	The Lyman-Kutcher-Burman model
LQ model	Linear quadratic model

MDR	Medium dose rate
MLC	Multi Leaf Collimator
MPR	Multiplanar reconstruction
MRI	Magnetic resonance imaging
NOCECA study	Nordic Cervical Cancer study
NSGO	Nordic Society of Gynecological Oncology
NTCP	Normal tissue complication probability
OAR	Organs at Risk
PDR	Pulsed dose rate
RTOG	Radiation Therapy Oncology Group
SD	Standard deviation
SOMA	Subjective objective management analytic
TCP	Tumour Control Probability
TPS	Treatment planning system
Vx	Volume of a structure covered by x isodose level

List of papers

I Hellebust TP, Kristensen GB, Olsen DR. Late effect after radiotherapy for locally advanced cervical cancer; comparison of two brachytherapy schedules and investigation of the impact of dose delivered per week. *Int J Radiat Oncol Biol Phys,* In press

II Hellebust TP**,** Tanderup K, Bergstrand ES, Knutsen BH, Røislien J, Olsen DR. Reconstruction of the ring applicator set using CT imaging; impact of reconstruction method and applicator orientation *Phys Med Biol* 2007;52:4893-4904.

III Tanderup K, Hellebust TP, Lang S et al Consequences of random and systematic reconstruction uncertainties in 3D image based brachytherapy in cervical cancer, *Radiother Oncol* 2008;89(2):156-163.

IV Hellebust TP, Dale E, Skjønsberg A, Olsen DR. Inter-fraction variation in rectum and bladder volumes and dose distributions during HDR brachytherapy treatment of the uterine cervix investigated by repetitive CT-examination. *Radiother Oncol* 2001;60:273-280.

V Dale E, Hellebust TP, Skjønsberg A, Høgberg T, Olsen DR. Modeling normal tissue complication probability from repetitive CT scans during fractionated HDR brachytherapy and external beam radiotherapy of the uterine cervix. *Int J Radiat Oncol Biol Phys* 2000;47:963-971.

1. Introduction

Radiotherapy plays a major role in the management of locally advanced cervical cancer. Both external beam radiotherapy (EBRT) and intracavitary brachytherapy (ICBT) are used, often in combination with chemotherapy. Radiotherapy is always a trade off between the dose that can be delivered to malignant tissue and the dose that can be tolerated by healthy tissue. To achieve local control, and subsequently patient cure, very high doses have to be delivered to patients with locally advanced cervical cancer. Traditionally this treatment has been rather toxic and it has been reported that up to 20 - 25 % of the patients experience serious adverse side effects [1]. To optimise the treatment of locally advanced cervical cancer it is important to establish a firm knowledge about dose response relationship in cervical tumours as well as in organs at risk (OAR).

Brachytherapy is delivered by placing hollow tubes (applicators) with radioactive sources in the cervix and in the top of the vagina. In this way the dose is confined locally to the tumour. The dose distribution around the sources is very inhomogeneous and the dose is rapidly decreasing as the distance from the sources increases. To be able to calculate the absorbed dose to the tumour and normal tissue, it is important to know the sources location in relation to adjacent tissue. This localisation process is guided by medical imaging. The presence of the applicators may alter the surrounding anatomy considerably. Consequently, for a correct dose calculation the images should be acquired with the applicator *in situ*. Traditionally, this process is performed by using a pair of x-ray images [2,3,4]. However, this method is hampered by the fact that irregularly shaped volumes cannot be precisely determined from conventional x-ray images. In 1985 International Commission on Radiation Units and Measurements (ICRU) published report 38 making recommendations on dose and volume specifications in intracavitary brachytherapy [5]. Two points were defined for reporting the dose to respectively the rectum and the bladder. However, the correlation between the dose to these points and late complications is controversial [6,7,8,9,10]. Three-dimensional treatment planning may provide more accurate dosimetry and improve correlation with organ-specific morbidity. In the GEC-ESTRO guidelines for management of radiotherapy for cervical cancer, it is recommended to use computer tomography (CT) or, preferably, magnetic resonance imaging (MRI) to localise the anatomical structures relative to the source positions [11]. At the Norwegian Radium Hospital CT imaging has been used for this purpose since 1998.

In 1994 the Norwegian Radium Hospital joined a study initiated by the Nordic Society of Gynecological Oncology. In this Nordic study with treatment of advanced cervical cancer (NOCECA study), the EBRT was standardised and the brachytherapy was delivered according to each hospital's institutional guidelines. A follow-up schedule was defined and scoring of morbidity was performed according to the Radiation Therapy Oncology Group/European Organization for the Research and Treatment of Cancer (RTOG/EORTC) [12]. The study was closed in 1999 and by that time the Norwegian Radium Hospital had included approximately 400 patients.

In this thesis acquired data from these patients, dosimetrical as well as follow up data, will be used to elucidate the relationship between severe complications and characteristics of radiotherapy for cervical cancer.

2. Cervix cancer

Carcinoma of the uterine cervix ranks high in mortality and morbidity world wide with high incidence rates particularly in developing countries. In Norway 294 new cases of invasive cancer of the cervix were diagnosed in 2006 [13]. The age-adjusted incidence rate per 100 000 person-years has been reduced from 11.3 in 1997 to 9.1 in 2006 [13]. The most frequently used classification system for cancer of the cervix is the FIGO (International Federation of Gynecology and Obstetrics) classification system [14], illustrated in Figure 1. The age-adjusted incidence rates in Norway per 1000 000 person-years by stage I-IV from 1953 to 2004 are shown in Figure 2. Even if the incidence is reduced, the yearly number of cervical cancer patients who receive radiotherapy at the Norwegian Radium Hospital has been unchanged in the last 6 years (unpublished).

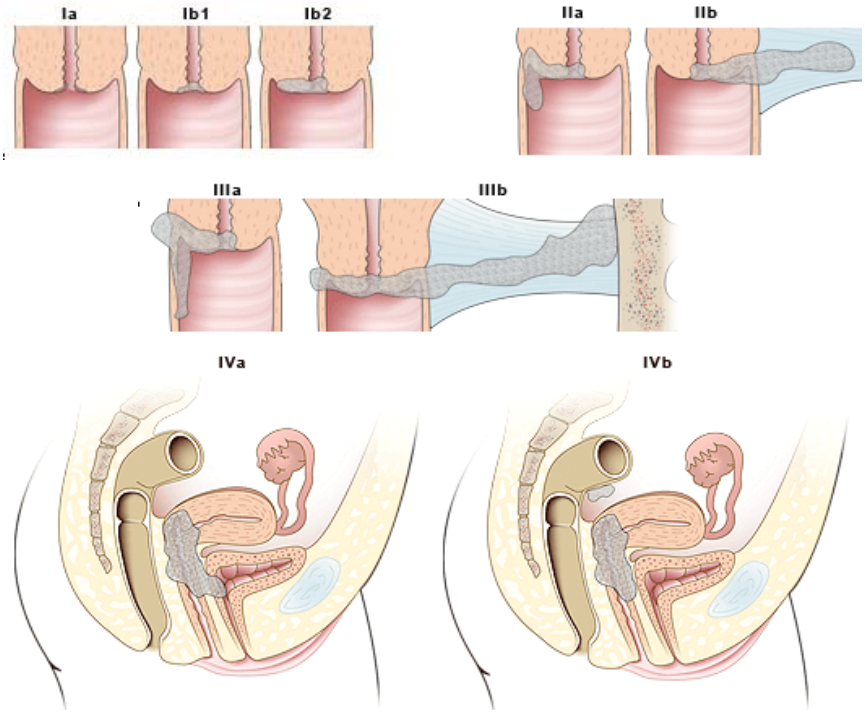

Figure 1. Illustration of FIGO classification system [15]

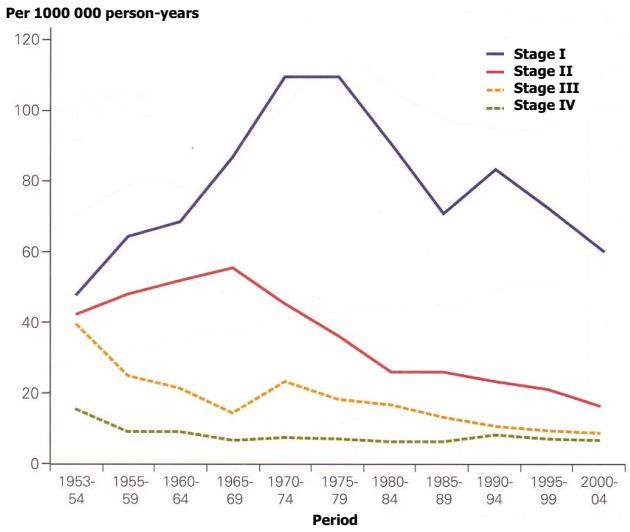

Figure 2. Age-adjusted incidence rate in Norway per 100 000 person-years from 1953 to 2004 by stage [16]

Cervical conisation with free margins or simple hysterectomy is adequate treatment for patients with cancer of the cervix stage Ia1 [17]. Patients with stage Ia2 and Ib1 patients are at higher risk for lymph node metastases. These patients are usually treated with radical hysterectomy (removal of the uterus with the lateral connective tissue; parametria) and removal of regional lymph nodes [18]. Radiotherapy comprising external beam irradiation and brachytherapy, usually in combination with chemotherapy, has been the preferred treatment for locally advanced disease as well as for bulky stage Ib. The outcome of patients with advanced carcinoma of the cervix is worse for patients who receive EBRT without brachytherapy [19]. In the period 1997-2001 the five years relative survival in Norway was 92.5 %, 62.7 %, 39.8 % and 9.7 % for stage I, II, III and IV, respectively [13].

3. External beam radiotherapy

External beam radiotherapy is delivered using linear accelerators. To treat cervical cancer, several high energy photon beams (> 10 MV) are usually applied to adequately give high dose to a centrally located target volume without giving too high doses to superficial structures in the pelvis. Two opposed anterior-posterior/posterior-anterior (AP-PA) fields in combination with two opposed lateral fields will most often give a homogeneous dose within the target and spare normal tissue. This treatment technique is usually referred to as four-field box technique. The dose distribution could be altered by changing the weight of each field and/or by applying wedges in one or several fields.

In the 90ths treatment planning in EBRT developed considerably and 3-dimensional (3D) treatment planning and conformal radiotherapy gradually became standard for EBRT [20]. Such treatment planning is based on a CT (or MRI) scan with the patient in treatment position and requires a computerised treatment planning system (TPS). The target volumes are delineated together with organs at risk (OAR). OARs are radiosensitive organs in or near the target volume which will influence the treatment planning or the prescribed dose. Several fields are individually shaped using multi-leaf-collimator or lead blocks in order to hit the target volumes and avoid OARs. In this way the dose distribution will be confined to the target volume and normal tissue will receive less dose than with a non-conformal technique. The last ten years Intensity Modulated Radiotherapy (IMRT) has been introduced and gives the opportunity to confine the dose even more to the target volume compared to conformal EBRT [20]. For the time being, IMRT plays an important role in EBRT for prostate cancer patients world wide. For cervical cancer patients, however, IMRT has not been implemented to the same extent, even though the technique has great potential in the future, especially in avoiding extensive dose to small bowel.

The concept and definition of target volumes in radiotherapy are published in a series of reports from ICRU. The gross tumour volume (GTV) is defined as the palpable or radiologically proven tumour [21,22]. Thus, for cervical cancer the GTV is defined as the tumour in cervix and adjacent tissue (GTV_{tumour}) as well as grossly enlarged lymph nodes (GTV_{nodes}). The clinical target volume (CTV) is defined as GTV plus suspected subclinical disease [21,22] and will for cervical cancer encompassed the GTVs and all pelvic lymph nodes. In general 45-50 Gy is considered to be an adequate dose to eradicate subclinical disease and in cervical cancer this dose is mainly delivered using external beam radiotherapy

(EBRT). However, to eradicate the GTV a larger dose is needed. This extra dose, the boost dose, to the grossly enlarged lymph nodes is usually given by EBRT while brachytherapy is used to boost the central part of the GTV.

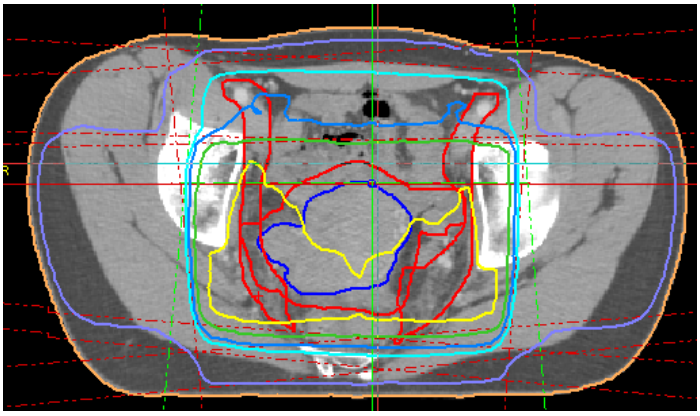

Figure 3. Dose distribution from EBRT of a cervical cancer patient. GTV (dark blue) and CTV (red) are delineated. The 50Gy and 45Gy-isodose is yellow and blue, respectively.

Figure 3 shows a typical dose distribution for a cervical cancer treatment with four-field box technique with additional two lateral fields. In order to quantitatively analyse the dose distribution, dose-volume histograms (DVH) are produced. The DVH is obtained by dividing

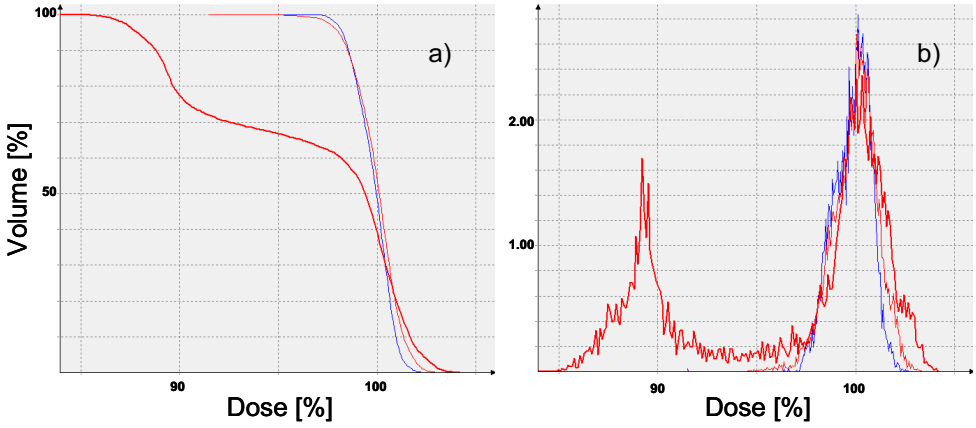

Figure 4. Cumulative (a) and frequency (b) DVH of GTV (blue) and CTV (red) from external beam radiotherapy of a cervical cancer patient.

the structure in question (GTV, CTV or OAR) into small volume elements and adding up the volumes at each dose level. By plotting these volumes as a function of dose a frequency dose-volume histogram is acquired (Figure 4a). A cumulative DVH is a plot of the volume receiving at least the dose D, as a function of D (Figure 4b). Clinically the latter DVHs are most often used to compare different treatment plans.

3.1. EBRT in the Nordic Cervical Cancer (NOCECA) study

In 1994 the Norwegian Radium Hospital joined a study conducted by the Nordic Society of Gynaecological Oncology (NSGO), the NOCECA study. The aim of this study was to investigate the pattern and rate of complications, recurrence rate and survival in patients with cancer of the cervix treated with the same external radiation, but different brachytherapy techniques and fractionations. Mainly patients with locally advanced cervical cancer (FIGO IIb-IVa) were included in the study.

Two CTVs were defined according to ICRU50 and 62 [21,22]: CTV-U encompassed the tumour, uterus and grossly enlarged iliac lymph nodes, while CTV-P included all other pelvic lymph nodes. CTV-P was treated to 45 Gy in 25 fractions, daily, through two AP-PA fields. The dose to CTV-U was raised from 45 to 50 Gy by an integrated boost of 0.2 Gy daily through two lateral fields encompassing only CTV-U. The fraction dose was thus 2 Gy to the uterus and enlarged lymph nodes and 1.8 Gy to the other pelvic lymph nodes. CT-based conformal treatment planning using block shaped fields was performed for each patient. Most patients were treated with AP/PA-fields and lateral fields as shown in Figure 5. In the AP/PA-fields, the upper border was usually located between L4 and L5 and the lower border usually 1 cm below the obturator foramen. Lateral borders were usually 2 cm beyond the widest pelvic bony brim.

The above described regimen was applied in patients with tumours ≤ 8 centimetres in diameter (Type A). The maximum planned treatment time was 6 weeks. In patients with tumours > 8 centimetres in diameter the dose of CTV-U could optionally be raised to 60 Gy by adding 10 Gy in 5 fractions to the lateral fields, with a maximal treatment time of 7 weeks (Type B).

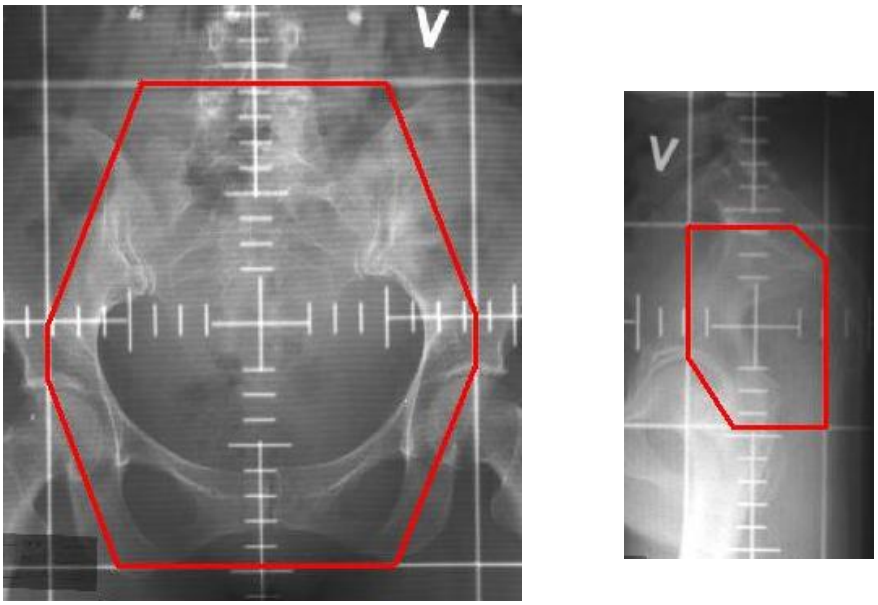

Figure 5. Example of AP-PA field (left) and lateral field (right) in the NOCECA study. The red lines indicate the field border.

4. Brachytherapy

Brachytherapy is radiotherapy using one or more sealed sources that are placed as close as possible to the site to be treated. When the source(s) is placed within a body cavity, such as the vagina, cervix or uterus, it is called intracavitary brachytherapy. Brachytherapy has been used in cancer treatment for more than a century and is the oldest radiotherapy modality. In the early days radium sources (Radium-226) were used and a number of different schools were developed, using slightly different application techniques and dose-rates. The most important schools in gynaecological brachytherapy, often referred to as systems, were the Manchester system, the Stockholm system and the Paris system [5]. Modern brachytherapy has evolved from these systems, but today there is a rather large difference between low-dose-rate (LDR) or medium-dose-rate (MDR) brachytherapy using mainly caesium sources (Caesium-137) and high-dose-rate (HDR) or pulsed-dose-rate (PDR) brachytherapy using iridium (Iridium-192). There are no universally accepted definitions of these dose-rate categories. However, ICRU has suggested the following definitions; LDR is 0.5-1.0 Gy/h, MDR is 1.0-12 Gy/h and HDR is above 12 Gy/h [5].

Usually hollow catheters (applicators) are placed inside the patient. When a proper position is verified by medical imaging, the source(s) is inserted. This technique is often referred to as afterloading technique. Traditionally, several sources were used in brachytherapy treatment and the afterloading was performed manually. In 1960 afterloading machines became available and offered the opportunity to automatically load the sources. The implementation of these machines lowered the staff exposure considerably. In the middle of the 80ths the brachytherapy equipment was developed even further and stepping-source devices became available. In this new generation of remote afterloading machines one single iridium source is attached to a flexible wire and is sequentially stepped through a series of dwell positions inside the applicator. The position of the source is controlled by a computer outside the treatment room.

In brachytherapy there is a rapid decrease of dose as the distance from the source increases. This means that brachytherapy gives the opportunity to deliver rather high dose to the target volume without giving too high dose to adjacent structures. However, this also means that the dose distribution in the target volume is highly inhomogeneous and without a proper dose specification under-dosage may occur. Therefore, in traditional brachytherapy the specified dose is usually the minimum target dose and the reference isodose is supposed to encompass the target volume and does not represent the average dose in the target volume, as in EBRT.

4.1. Treatment planning in traditional brachytherapy

Treatment planning in traditional brachytherapy is usually based upon conventional x-ray imaging, often a pair of orthogonal images. From such images it is impossible to fully reconstruct a 3D structure. Thus, the dose specification has to be based upon one or several points. The Manchester system defined such a reference point, point A. Point A was defined as being 2 cm lateral to the centre of the uterine canal and 2 cm superior to the bottom of the uterine source tube, measured along the longitudinal axis of the tube [23]. The dose to point A was supposedly representative of the minimum dose to most of the malignant tissue when treating cervical cancer. Wilkinson et al emphasise that point A is a geometrical and not an anatomical point and that it can only be defined in a reference geometry [23]. Point A has been widely used worldwide and results from a survey distributed among European brachytherapy centres showed that 82 % of the replying departments still used point A for dose specification in 1998 [24]. Even if the use of point A has resulted in a certain degree of

consistency in dose specification, dose to a point will poorly describe the dose distribution to a target volume in brachytherapy.

In 1985 ICRU published a recommendation for dose specification and reporting in gynaecological brachytherapy [5]. In this report it is pointed out that the concept of maximum, mean and median dose is irrelevant due to the steep dose gradient that is present in brachytherapy. Specification of an intracavitary application in terms of the "reference volume" enclosed by the reference isodose was recommended, as well as reporting of the total reference air kerma [5]. The concept of "reference volume" had evolved from the classical LDR brachytherapy and Pötter et al showed that this concept has been poorly implemented in departments using HDR Brachytherapy [24].

The ICRU report 38 also included recommendations for reporting absorbed dose to organs at risk (OAR) [5]. A reference point was defined for both the bladder and the rectum [5]. The bladder reference point is found by using a Foley catheter in the bladder. An anterior-posterior line is drawn through the centre of the balloon on a lateral x-ray image. The reference point is found on this line at the posterior surface of the balloon. On a frontal image the point is located at the centre of the balloon.

The ICRU rectum reference point is also found from a lateral x-ray image where an anterior-posterior line is drawn from the lower end of the uterine source (or from the middle of the intravaginal sources). The point is located 5 mm posterior of the vaginal wall on this line. On a frontal image the point is found at the lower end of the intrauterine source or at the middle of the intravaginal sources. The concepts for both the bladder and the rectum reference points are illustrated in Figure 6.

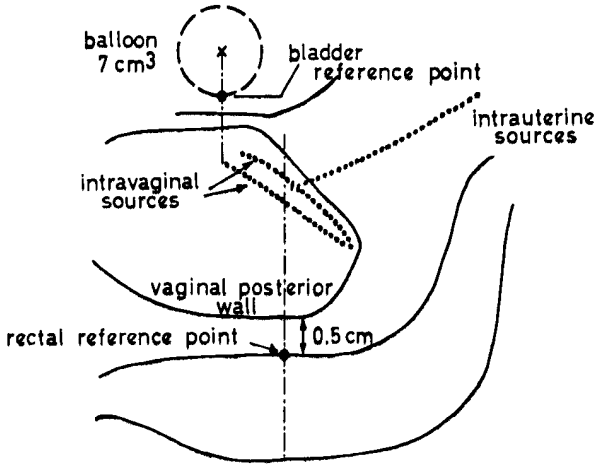

Figure 6. Definition of the ICRU rectum and bladder reference point [5].

Due to the steep dose gradients in brachytherapy the absorbed dose in one single point would not represent the total exposure of these organs. Additionally, the ICRU points do not provide any information on the volume of the organ that is irradiated to significant dose levels. For the last 10-15 years it has become evident that dose-volume relationships are important for assessing the probability of complications in many OARs. It is not possible to establish this kind of data by using conventional 2D imaging. 3D based treatment planning is needed.

4.2. Treatment planning in modern brachytherapy

In the middle of the 90ths tools for 3D-based treatment planning were implemented into TPSs for brachytherapy and provided the opportunity to perform individualised planning based on CT or MR imaging. However, implantation of modern treatment planning has been slow and still a lot of departments are using 2D-based treatment planning [25].

4.2.1. Delineation, dose specification and reporting

In 2000 a group within GEC-ESTRO was established with the task to describe basic concepts and terms in 3D-based gynaecological brachytherapy and to recommend a framework of terminology within this field. Such a terminology would enable various groups working in gynaecological brachytherapy to use a common language for communicating their results.

In 2005 and 2006 Heie-Meder et al and Pötter et al published GEC-ESTRO recommendations on concepts and terms in 3D image based treatment planning for brachytherapy of cervical cancer [11,26]. In the first publication the concept of high risk CTV (HR-CTV) and intermediate risk CTV (IR-CTV) was presented. In this concept the tumour volume at the time of brachytherapy as well as at the time of diagnosis are taken into account to define the GTV and the CTVs. This is the first publication that on a systematically basis recommends delineation of target volumes in cervical brachytherapy. It is recommended that the target delineation should be MR-based, while delineation of OARs could be performed either in MR or in CT images [11]. In the second publication the concept of using DVH in brachytherapy is described. Recommendations are given on DVH parameters to be used for dose specification and reporting in order to create a common language.

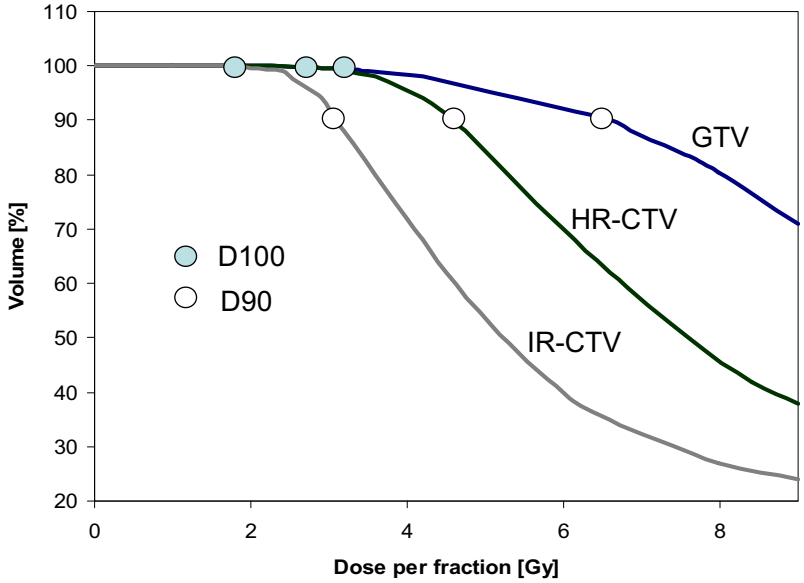

Figure 7. Typical dose-volume-histograms for GTV, HR-CTV and IR-CTV

A typical brachytherapy DVH of a target volume have a plateau (Figure 7), indicating 100% dose coverage of a certain volume. The coverage of the target volume can be described by specifying a dose level that covers a certain percentage of the target, e.g. D100 and D90, defining the minimum dose delivered to 100 and 90 % of the target, respectively. The D100 is very sensitive to inaccuracies in the delineation and D90 is therefore considered to be a more robust parameter. However, it is recommended to report both parameters [26]. Volumes of certain dose levels could also be reported. The dose levels could be given either as an absolute number or as a percentage of the prescribed dose. The volume of the 200 % and 300 % isodose, V200 and V300, will together give an indication of the gradient inside the prescribed isodose.

Typical severe late complications after gynaecological brachytherapy are fibrosis, ulceration, necrosis and fistulas. When assessing such severe late effects it seems like small organ volumes irradiated to high doses are important [26]. A volume of 1-2 cm^3 tissue corresponds to the size of a fistula. Thus, DVHs with absolute volumes on the y-axis should be used for evaluating dose distribution in OARs after combined treatment with brachytherapy and EBRT, in contrast to EBRT alone where relative DVHs are usually used. In a relative DVH the volume one the y-axis is given as a fraction of the total organ volume.

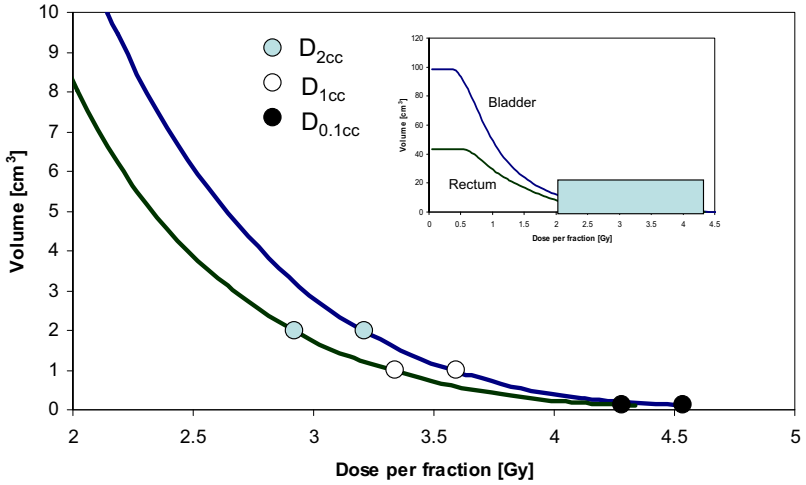

Figure 8. Typical Dose-volume-histograms for organs at risk in brachytherapy

The minimum dose in the most irradiated 0.1, 1, 2 and 5 cm^3 volume is recommended for recording and reporting [26]. These parameters are usually denoted $D_{0.1cc}$, D_{1cc}, D_{2cc}, and D_{5cc} and are found in the upper part, or the "tail", of the DVH curve (Figure 8). For volumes less than 2-3 cm^3 the DVH parameter for the whole bladder and rectum (including the filling) is approximately the same as for the organ wall [27,28] and delineation of the outer organ contour is sufficient.

When whole organ late effects like overall organ inflammation or teleangiectasia are being assessed, the whole dose distribution in the organ and the whole DVH most probably also have to be evaluated.

4.2.2. Applicator reconstruction

Calculating dose to anatomical structures, it is necessary that the geometry of the applicator and the source dwell positions are transferred from the images with the applicator *in situ* to the TPS; a process often referred to as applicator reconstructing. Performing treatment planning using sectional imaging is very different from the traditional method using x-ray imaging. With the latter technique the track of the source is found by using an x-ray markerstring and projection images, and all points could easily be reconstructed. The use of sectional images in the applicator reconstruction process is, on the other hand, more challenging.

Inaccuracy in the reconstruction process could potentially lead to geometrical uncertainties and thus uncertainties in definition of source positions. These uncertainties may alter the calculated dose distribution to both target volumes and OAR. Hence, it is important to investigate the uncertainties in this step of the treatment planning process.

Pre-clinical applicator commissioning is important. During commissioning the location of the dwell positions is found in relation to each other or in relation to a reference point in the applicator, e.g. the distance from the tip of the tandem applicator to the first dwell position. The geometry of the applicator, or more correctly the relative location of the source dwell positions, can then be stored as library files and later used clinically. The clinical procedure for importing such library files is critical. It is important to realise that even a geometrically correct applicator that is wrongly positioned in the 3D study will lead to an incorrect estimate of the dose distribution in the patient. At least three well defined points have to be identified in the applicator in order to merge the library file with the clinical 3D study (Figure 9). This reconstruction method is usually referred to as the library reconstruction method (LIB).

The applicator could also be reconstructed by digitising the track of the source directly in the acquired images (direct reconstruction, DR). When using this method it is important to correctly identify the first dwell position. If the first dwell position is located between two images a correction should be applied. When transversal (or para-transversal) images are used a lateral view is a valuable tool to determine the magnitude of this correction. Even if the first dwell position is correctly identified it is also important to correctly digitise the track of the source. When digitising a curved applicator in several images there is an inherent risk of reconstructing a too long or too short track. When many points are used a tagged shaped applicator is often the result (Figure 9). Consequently the dwell positions will be located wrongly with a potential result of inaccuracies in the dose distribution.

Today TPSs in brachytherapy offer the possibility of producing so called multiplanar reconstruction (MPR) images. This means that an image can be reconstructed in any plane based upon the originally acquired images. The quality of these MPR images depends on the distance between the original images. MPR images can be a very useful tool in the reconstruction process. If the relevant part of an applicator, e.g. a ring applicator, could be visualized in one single MPR image, the problems with the direct reconstruction (DR) described above, could be avoided (Figure 9). Since the quality of the MPR images is some

times a limitation, the reconstruction of straight, rigid applicators should preferably be performed by using the DR method.

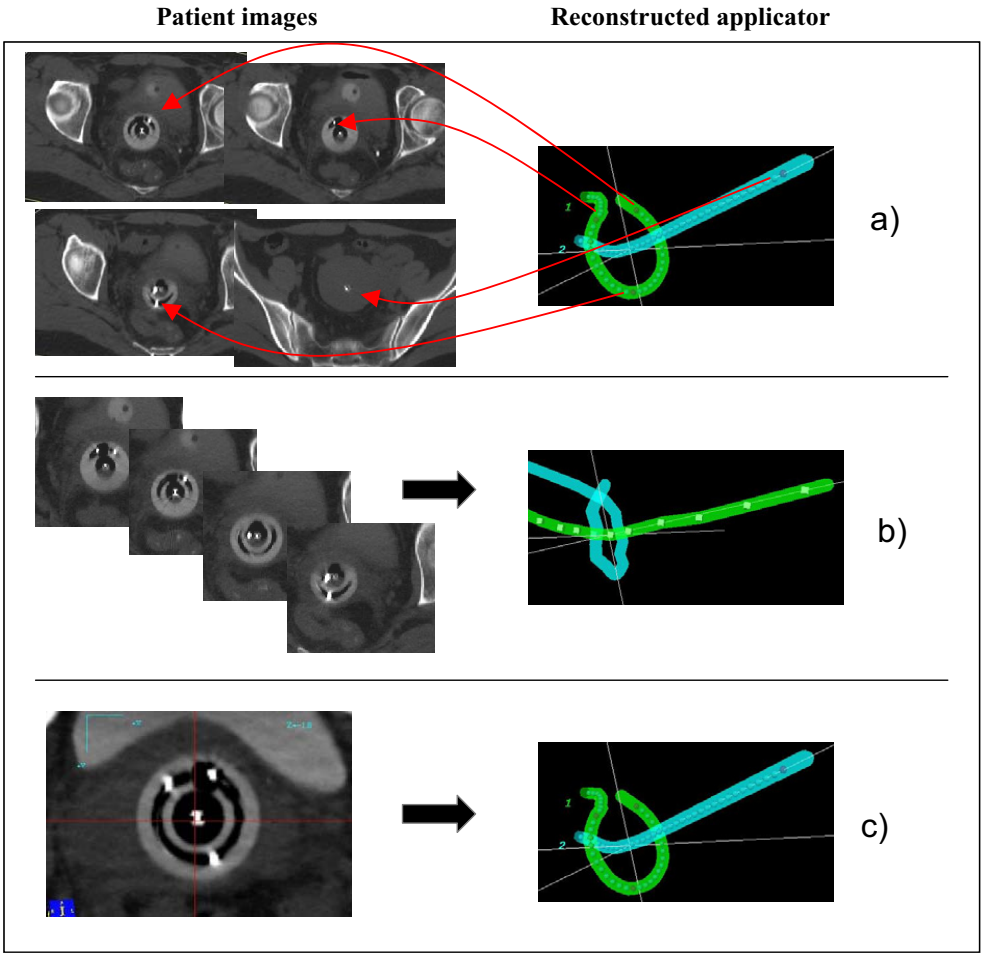

Figure 9. Illustration of different reconstruction methods using a) library file (LIB), b) direct reconstruction (DR) and c) multiplanar reconstruction images (MPR).

5. Normal tissue complication

Radiotherapy of deep-seated tumours is inevitably accompanied with normal tissue doses to some extent. If the dose is sufficiently high or the irradiated volume large, normal tissue complications will occur.

5.1. Classifications of normal tissue complications

Usually normal tissue complications are divided into two categories according to time of onset of the clinical symptoms. Early effects are seen in tissues with rapid cell proliferation, such as intestinal epithelium, bone marrow, and skin. Early effects are observed during the course of treatment or within a few weeks after treatment, and they are most often transient. Late (≥ 90 days) effects of radiation damage appear in tissues with a slower turnover of cells, such as subcutaneous tissue, brain, kidney, liver, and the intestinal wall. Late effects are usually irreversible and often progressive. Additionally, the fractionation sensitivity is high, i.e. increased dose per fraction for a given total dose, will significantly increase the severity and frequency of the effects [29,30]. In general there is no correlation between the early and late complications in individual patients. However, in some tissues and organs late effects may occur as a consequence of severe early reactions. These types of complications are referred to as consequential late effects (QLE) [31].

Normal tissue effects are also classified according to the severity of the complications and several systems for grading and reporting are available. None of these has so far gained general acceptance, although the RTOG/EORTC Late Morbidity Scoring Criteria [12] has been used extensively. In 1995, the RTOG/EORTC working groups on late effects of normal tissues proposed the LENT/SOMA system [32,33]. Several publications show that it is feasible to use this system. The general impression, however, is that it is time-consuming, which may hamper wide implementation in clinical practice. Both of these two systems are grading the normal tissue complications on a 1-4 scale, with 1 corresponding to mild morbidity and 4 to life threatening morbidity. Grade 0 may be used for no complications and grade 5 for complication-related death. “Increased frequency or change in quality of bowel habits not requiring medication” and “Acute or subacute obstruction, fistula or perforation” are examples of grade 1 and 4 morbidity of the lower gastro intestine, respectively [12]. Corresponding examples of late effects of the bladder are “Slight epithelial atrophy or minor

teleangiectasia (microscopic hematuria)" and "Necrosis/Contracted bladder or severe hemorrhagic cystitis" [12].

5.2. Fractionation

A continuously bending cell survival curve can be fitted by a second-order polynomial, with a zero constant term:

$$S = e^{-\alpha d - \beta d^2} \quad (1)$$

where S is the cell survival fraction and d is the dose. α and β are cell specific parameters. By assuming that each successive fraction in a multi-dose schedule is equally effective the survival of n fractions with the dose d will be:

$$S = e^{-n(\alpha d + \beta d^2)} \quad (2)$$

These equations are referred to as the linear quadratic (LQ) model [30,34]. If the radiobiological effect is expressed as E = -ln(S), the equation will become:

$$E = n(\alpha d + \beta d^2) = \alpha D + \beta d D \quad (3)$$

where D is the total dose. The LQ model is extensively used worldwide in both experimental and clinical radiobiology and generally works well in describing response to radiation both *in vitro* and *in vivo* [35]. Equation 3 could be rearranged into the following form, expressing biologically equivalent dose (BED):

$$\mathrm{BED} = \frac{\mathrm{E}}{\alpha} = \mathrm{nd}\left(1 + \frac{\mathrm{d}}{\alpha/\beta}\right) \quad (4)$$

The BED is used to compare different fractionation schedules clinically. Irradiating a biological system with the fraction dose d in n fractions is assumed to have the same biological effect as irradiating the system over an infinitely long time with the total dose BED. This concept can sometimes be difficult to understand. A more clinically familiar expression will be to convert the total dose into an equivalent schedule in 2 Gy fractions (EQD_2):

$$\mathrm{EQD}_2 = \mathrm{D}\frac{\mathrm{d} + (\alpha/\beta)}{2 + (\alpha/\beta)} \quad (5)$$

A number of clinical studies have produced estimates of α/β-ratio for human end-points [36], but often 10 and 3 are used for early and late reacting tissue, respectively.

The LQ-model is an empirical model, but it has been suggested that the α-term in equation 1 represents the single-track events (single strand break) in the DNA molecule, while the β-term represents the two-track events (double strand break) [35]. However, it is very unlikely that two tracks interact within the dimensions of the DNA molecule at a dose of a few Gy [35]. Another way of explaining radiation cell killing is by assuming that there exists a specific region of the DNA that are important to maintain the reproducibility of the cell. This region could be considered to be a target within the cell and the survival of the cell would be related to the number of targets inactivated. This theory is usually referred to as the target theory and the probability of cell survival could be described by using Poisson statistics [35].

5.3. Modelling normal tissue complication probability

Before treating a patient it would be very convenient if we were able to estimate the expected tumour control probability (TCP) and normal tissue complications probability (NTCP) for a specific dose level. Several mathematical models have been suggested in the literature for calculating TCP and NTCP-values. These models can in general be divided into two groups; empirical and mechanistic models. The first types of models are not based upon any underlying biological assumptions, but use mathematical expressions that are fitted to observed data. The functional models, on the other side, aim to describe the relation between the departed energy and the biological response and include parameters that are based upon biophysical principles. Often many parameters are included in these models and they are usually complex.

Lyman was the first to formulate a mathematical relationship between dose, volume and NTCP [37]. He assumed a power law dependence of a partial organ irradiation of volume fraction v:

$$TD_c(v) = \frac{TD_c(v=1)}{v^n} \qquad (6)$$

where TD_c is the tolerance dose for c % probability of a certain endpoint or complication to occur and n is a parameter describing the volume dependence [37], e.g. $TD_{50}(1)$ will be the tolerance dose for 50 % probability of a certain endpoint when the whole organ is irradiated.

Lyman also assumed a sigmoid relationship between dose and complication probability. Thus, the mathematical expression of the NTCP could be found through integration of the normal distribution:

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-\frac{x^2}{2}} dx \qquad (7)$$

where

$$t = \frac{D - TD_{50}(v)}{m \cdot TD_{50}(v)} \qquad (8)$$

and m is the slope parameter determining the inclination of the NTCP curve [37].

Burman et al reported volume dependence of the complication probability for 28 organs and estimated TD_{50}, n and m based on these data [38].

The Lyman model was developed for uniform irradiation of whole or partial organ. The model has later been modified in order to include inhomogeneous irradiation by applying a histogram reduction technique to the DVH to obtain a risk-equivalent DVH corresponding to homogeneous, partial organ irradiation:

$$v_{eff} = \sum_{i=1} v_i \left(\frac{D_i}{D_{\max}}\right)^{\frac{1}{n}} \qquad (9)$$

where D_i is the dose to the fractional volume element v_i and v_{eff} is the effective volume fraction [39,40,41]. If v_{eff} receives D_{max} the resulting NTCP will be the same as for the original DVH. The model including the DVH reduction algorithm is usually referred to as the Lyman-Kutcher-Burman (LKB) model.

Mohan et al suggested another histogram reduction technique that defined an effective dose instead of an effective volume. The effective dose was defined as “the dose that the entire volume (V=1) uniformly receives to produce a complication probability equal to that for inhomogeneous irradiation” [42]. The mathematical expression was based on the power law dependence, a type of relationship that has been observed in many biological phenomena:

$$D_{eff} = \left(\sum_{i=1} v_i (D_i)^{\frac{1}{n}}\right)^n \qquad (10)$$

This is the same expression as the generalised equivalent uniform dose (gEUD) suggested by Niemierko et al [43] and Wu et al [44]. In the gEUD expression a (= 1/n) is used as the tissue-specific parameter that describes the dose-volume effect.

6. Aim of the study

Treatment planning in brachytherapy for cervical cancer has rapidly developed for the last ten years and now days many centres have changed from 2D to 3D image based treatment planning. 3D image guided brachytherapy integrates modern imaging and advanced computer technology in a new approach. However, the introduction of this new concept has raised many questions about the benefit and reliability of the procedure. The overall aim of this thesis is to address important aspects regarding the introduction of 3D image based HDR brachytherapy for cervical cancer patients with severe late complications in focus.

Specific aims:

- To investigate whether the dose to Point A [23] or the ICRU reference points [5] could predict severe late effects in cervical cancer patient treated with a combination of EBRT and ICBT.
- To investigate whether there exists an upper limit for the dose delivered each week to avoid rectum and bladder complications with a combination of EBRT and ICBT
- To determine the accuracy of the ring applicator reconstruction using 3D imaging and investigate the impact of these uncertainties on DVH parameters.
- To investigate the reproducibility of HDR brachytherapy and whether there exists a relationship between organ volume and organ dose for cervical cancer patients.
- To calculate NTCP values of rectum and bladder using an established model and compare these values with clinically derived complication frequencies.

7. Method and design

7.1. Nordic Cervical Cancer (NOCECA) study at the Norwegian Radium Hospital

The Norwegian Radium Hospital started to include patients in the NOCECA study in 1994. Until October 1996 the ICBT delivered 33.6 Gy in 8 fractions (Type A treatment) or 25.2 Gy in 6 fractions (Type B treatment). An intermediate analysis indicated that the incidence of adverse side effects was too high and from October 1996 the total dose delivered with ICBT was reduced to 29.4 Gy in 7 fractions for Type A and 21 Gy in 5 fractions for Type B treatment.

The majority of the patients were treated with a ring and tandem applicator with a standardised source configuration forming the classical pear shaped isodoses. The dose was prescribed to point A [23]. A rectal retractor was used to push the rectum away from the high dose area. Some patients were treated with an intrauterine tube in combination with a vaginal cylinder. The dose was then prescribed to a point 5 mm from the surface of the vaginal cylinder.

Until November 1997 the patients were treated with a ^{60}Co-Selectron afterloading machine (Nucletron BV, Veenendaal) while a MicroSelectron machine with a stepping ^{192}I source was used (Nucletron BV, Veenendaal) subsequently. Standard plans for treatment with the stepping source device were elaborated to match the dose distribution for the ^{60}Co-Selectron standard plans.

The EBRT was delivered by using two AP/PA fields giving 45 Gy in 25 fractions to the whole pelvis. In each fraction 0.2 Gy was delivered by two opposed lateral fields to the GVT, resulting in 50 Gy in 25 fractions.

The patients were seen for follow-up every three months the first year, every sixth month the second and third year and then once yearly until five years after treatment. The visits included examination for relapse and physicians' scoring of morbidity according to the Radiation Therapy Oncology Group/European Organization for the Research and Treatment of Cancer (RTOG/EORTC) late radiation scoring scheme [12].

7.2. Analysis of severe late effects in two different ICBT schedules

Only patients that strictly followed the Type A treatment were included in the analysis. 119 patients from the first period (high dose group, HDgroup) and 120 from the last period (low dose group, LDgroup) were included. The cumulative incidences of severe (≥ grade 3) gastrointestinal (GI) and genitourinary (GU) late effects were calculated for both the HD- and LDgroup using the Kaplan-Meyer method.

To investigate whether there exists an upper dose limit that could safely be delivered within a week without increasing the probability of severe late effects, the dose per week was calculated for each individual patient. Thereafter the number of weeks with dose higher than 14 Gy, 16 Gy, 18 Gy and 20 Gy were identified on an individual patient level. Since the dose per week is a sum of dose from EBRT and ICBT, the number of weeks with EQD_2 higher than 14 $Gy_{\alpha/\beta=3}$, 16 $Gy_{\alpha/\beta=3}$, 18 $Gy_{\alpha/\beta=3}$ and 20 $Gy_{\alpha/\beta=3}$ were also calculated. Kaplan-Meier method with log-rank test was used to analyze these data.

7.3. Applicator reconstruction accuracy

To quantify the accuracy in applicator reconstruction using the ring applicator set and CT imaging, a ring applicator set was scanned four times with the ring plane orientation 0°, 10°, 20° and 30° relative to the image plan. Slice thickness of 3 mm was used to scan the ring while 5 mm slice thickness was used above and below the ring. During the CT acquisition the applicator set was submerged in a phantom filled with gelatine gel (Gelita, Eberbach). The applicator was reconstructed using the LIB, DR and MPR method (Figure 9) and the doses to six well defined points (lead pellets) around the applicator were calculated using Plato version 14.2 (Nucletron BV, Veenendaal).

To determine the impact of the applicator reconstruction uncertainties on clinical DVH parameters, dose distributions from 20 cervical cancer patients with MRI based brachytherapy planning were analysed. These patients were all treated at the General Hospital of Vienna. The EBRT was delivered with a total dose of 45 Gy in 25 fractions, while the brachytherapy was delivered in 4 fractions with total dose of 28 Gy. Ten patients were treated with an MRI compatible ring applicator set. The remaining 10 patients were treated with a combined interstitial and intracavitary ring applicator set with drilled holes in the periphery of the ring, allowing to insert needles into the tumour [45]. The target volumes and the OAR were delineated in the MR images according to the GEC-ESTRO recommendations [11,26] and

manual 3D dose planning was performed to optimise dose coverage of the target and to spare OARs.

Applicator reconstruction uncertainties were simulated by shifting the dose distribution in relation to the delineated structures and calculating the impact on the DVH parameters. The dose distributions were shifted ± 3 mm in three directions: along the tandem applicator, transversal and anterior-posterior. Along the tandem applicator the dose distribution was also shifted ± 5 mm. Finally, ± 15° rotation of the ring was applied in the transversal plane.

7.4. Inter-fractions variation analysis and NTCP calculations

The analyses in Paper IV-V are based on the same patient cohort. This cohort comprises fourteen patients treated with combined EBRT and ICBT. Eight and three patients were treated with EBRT according to Type A and B treatment, respectively and they received 7 and 5 fractions of ICBT. The remaining three patients had enlarged para-aortic lymph nodes and were treated with a 4-field box technique. The upper borders for all these fields were most often between the T12 and L1 disc. In these cases all the fields were weighted equally and the patients received 50.4 Gy in 28 fractions. The ICBT was delivered in 7 fractions with a total dose of 29.4 Gy to point A. (For further details see Table 1 in Paper V.)

All patients underwent CT examination with the applicator *in situ* in 3-6 of the ICBT treatments. The whole bladder and rectum, as well as the wall of the organs were delineated in all the acquired CT studies and the DVHs were calculated using the Plato system (Nucletron BV, Veenendaal, IPS 2.6, Eval 2.3, BPS 13.7).

The inter-fraction variations (1SD) in different DVH parameters were calculated for each individual patient. Correlations between organ volumes and time after start of treatment as well as correlations between organ volumes and dose were also investigated.

NTCP values were calculated using the LKB-model (section 5.3) for each patient based on the total DVH. The total DVH was estimated by summing doses of equal volume fractions from each cumulative DVH. The dose to each volume fraction was converted into EQD_2 according to equation 5 before the summation.

8. Summary of results

8.1. Paper I

In this study severe late effects (≥ grade 3) for two groups of cervical cancer patients treated with the same external beam radiotherapy and two different high-dose-rate intracavitary brachytherapy (ICBT) regimes were investigated. Kaplan-Meier method with log-rank test did not show any significant different cumulative incidence in severe late GI and GU complications for the patients in these two groups.

The Kaplan-Meier method with log-rank test revealed that there was a marginally significant lower cumulative incidence of GI and GU complications for patients with no weeks with dose higher than 20 Gy compared to patients with one or two weeks with dose higher than 20 Gy ($p = 0.047$) in the HDgroup. The same analysis did not show any significant differences for the other dose levels that were tested for any of the groups.

8.2. Paper II

In this study the reproducibility of applicator reconstruction using CT images was investigated. A ring/tandem applicator, submerged in a gel phantom, was scanned four times with the ring plane orientation 0°, 10°, 20° and 30° relative to the image plan. In these four set of CT images the applicators were reconstructed using 1) direct reconstruction (DR), 2) multiplanar reconstruction images (MPR) and 3) the library plan method (LIB). The influence of the applicator orientation and reconstruction on dose distribution was evaluation by calculating the dose to six well defined points in the phantom. The results show that the smallest and largest variation in dose calculation to these points is seen close to the tandem and the ring applicator, respectively. This is logic, since the ring applicator is expected to be more influenced by reconstruction method and applicator orientation than the tandem. No applicator orientation could be identified as more reproducible than the others. If the applicator orientation is not standardised, the LIB method is the most reproducible way of reconstructing the applicator. However, for all the methods and all the calculation points the relative standard deviation were equal to or smaller than 3.7 %, indicating that the uncertainties due to applicator reconstruction is small compared to other factors influencing the accuracy of brachytherapy.

8.3. Paper III

The impact of applicator reconstruction uncertainties on DVH parameters was investigated for cervical cancer patients: 10 patients treated with intracavitary brachytherapy and 10 patients treated with a combined interstitial and intracavitary technique. The dose distributions were optimised by aiming at maximal coverage of the target volume and a reduction of doses to OARs. Applicator reconstruction uncertainties were simulated by shifting the dose distribution in relation to the delineated structures. The dose distributions were shifted ± 3 mm in the transversal direction and in the anterior-posterior direction. Additionally the dose distribution was shifted ± 3 mm and ± 5 mm along the tandem applicator. Finally, ± 15° rotation of the ring was performed in the transversal plane. DVH parameters were calculated for each translation and rotation.

The results showed that the impact of the uncertainties was most pronounced in the anterior-posterior direction for the rectum and bladder with a mean of approximately 5 % change in the D_{2cc} per mm dose distribution displacement. The impact of uncertainties in the longitudinal direction (along the tandem applicator) was largest for rectum with a mean of 3.5 % change in the D_{2cc} per mm dose distribution displacement for all the patients.

The consequences of random and systematic reconstruction uncertainties was analysed further by assuming a normal distribution of the uncertainties with the mean being equal to systematic errors and the variance representing the random errors. Also the slope was assumed to be normally distributed, with the mean and the variance estimated from the slope distribution from the 20 patients. 10 000 simulations were performed and the results showed that systematic errors of only a few millimetres will be followed by significant changes in the DVH parameters. By avoiding systematic reconstruction errors, uncertainties on DVH parameters can be kept below 10 % in 90 % of a patient population.

8.4. Paper IV

The aim of this study was to quantify the inter fraction variations of dose volume related parameters for patients receiving fractionated high dose rate brachytherapy. Correlations between organ volumes and time after start of treatment as well as correlations between organ volumes and dose were also investigated. CT scans with the applicator *in situ* from sixty-nine treatments of fourteen patients (three to six fractions per patient) were analysed. For each fraction the volume of rectum, rectum wall, bladder and bladder wall were calculated. Additionally the clinically relevant maximum dose and the median dose for these volumes

were found from the relative dose volume histograms. For each patient series the average value and relative standard deviation (coefficient of variance, CV) for the volume of the rectum and bladder were calculated. To quantify a general inter fraction variation a mean CV was calculated for all the patients. CV_{mean} was 23.3 % and 44.1 % for the rectum and bladder volume, respectively. The inter fraction variation of the bladder volume was not accompanied by a corresponding variation in dose, since CV_{mean} for the clinically relevant maximum dose (17.5 %) and the median dose (19.9 %) to the bladder wall were significantly lower than CV_{mean} for the whole bladder volume ($p < 0.05$). The same trend, although not significant, was seen for rectum, with CV_{mean} of 15.0 % for the clinical maximum dose ($p = 0.14$) and 16.5 % for the median dose ($p = 0.12$) to the rectum wall.

The rectum volume was not correlated with time after first treatment while the bladder volume significantly reduced ($p = 0.018$) throughout the treatment.

A linear regression analysis showed a significant correlation between the organ volume and the median dose, both for rectum ($p = 0.003$) and bladder ($p = 0.001$). However, the analysis did not show any correlation between the organ volume and the clinical maximum dose for neither of the organs.

8.5. Paper V

The normal tissue complication probability (NTCP) was calculated for fourteen patients (same patient cohort as in paper III) treated with 25 fractions of external beam radiotherapy and 5-7 fractions of intracavitary high dose rate brachytherapy. Dose-volume-histograms from multiple fractions were corrected for variable dose per fraction and then summed to create a total DVH, representing an estimate of the whole course of treatment. The LKB model fitted to clinical dose-volume tolerance data was used to calculate the NTCP for the rectum and bladder. Using $n = 0.06$, $m = 0.15$ and $TD_{50}(1) = 80$ Gy the calculated NTCP of the rectum was 19.7 %, whereas the clinical frequency of severe late rectal complications (≥ grade 3) was 13 % based on a material from 200 patients. For the bladder the calculated NTCP was 61.9 % using $n = 0.13$, $m = 0.11$ and $TD_{50}(1) = 62$ Gy as compared to the clinical frequency of severe late effects of 14 %. A sensitivity analysis showed that the deviation between the calculated and observed frequencies of severe late effects in the rectum could be explained by uncertainties in the LKB parameters. This was, however, not the case for the bladder.

When only the CT study from the first fraction of brachytherapy was used as the basis for the NTCP calculation, the relative uncertainty (1SD) of the result was 20 and 30 % for the

rectum and bladder, respectively. Using CT studies from 4 fractions the uncertainties was found to be 12 % for the rectum and 13 % for the bladder.

9. Discussion

9.1. Predictive factors for late complications using 2D-based brachytherapy

Brachytherapy is an old radiotherapy modality and has been practiced since the beginning of the last century. Throughout the years several schools evolved in Europe and each of them developed a set of rules on how to perform the application and how to specify and report the treatment [5]. These schools are often referred to as systems. The image modality, if any, used for evaluation and verification of the implant in these systems was x-ray projection imaging. Such imaging does only allow point dose specification and it is not possible to delineate neither target volumes nor organs at risk (OAR). To harmonise the brachytherapy in gynaecological cancer ICRU published in 1985 recommendations for dose specification and reporting in gynaecological brachytherapy [5].

To report the delivered dose to OAR, bladder and rectum reference points were defined by ICRU [5]. The dose to these points was supposed to be of clinical relevance. Often the maximum dose to the rectum and bladder is considered important and several authors have pointed out that the ICRU reference points do not generally represent the maximum dose to the bladder and rectum [27,46,47,48,49,50]. However, better correlation is found between the maximum dose to the rectum and the ICRU rectum point than for the maximum dose to the bladder and the ICRU bladder point [48,51,52]. The ICRU reference points are, however, *not* supposed to represent the maximum dose to the bladder and the rectum. The absorbed dose to these points is on supposed to correlate with late complications of the organs in question [5]. It is generally accepted that this is not true for the bladder [8,53,54]. However, there exist some controversies with regard to the correlation between the dose to the ICRU rectum point and the late rectal complications. Some studies confirm this correlation [6,7,9,53,54,55,56,57,58,59], while other publications fail to show any [8,10,60,paper I]. The studies that do find a correlation are, however, not consistent with regard to what threshold to recommend. Noda et al found that there were significantly more late complications in the group of patients that received a BED of more than 140 $Gy_{\alpha/\beta=3}$ to the ICRU point compared to the group that received less ($p = 0.009$) [6]. A BED of 140 $Gy_{\alpha/\beta=3}$ corresponds to EQD_2 = 84 Gy (chapter 5.2). On the other hand, Cheng et al showed that a BED higher than 110 $Gy_{\alpha/\beta=3}$ to the ICRU reference point gave a significant difference in the incidence of late

effects (≥ Grade 2) in the rectum compared to lower values of BED (p = 0.022) [59]. A BED of 110 $Gy_{\alpha/\beta=3}$ corresponds to EQD_2 = 66 Gy (chapter 5.2). Ferrigno et al tested the same threshold as Cheng et al and did not find any significant difference in late rectal complications between patients that received rectum dose (ICRU reference point) above and below this value [8]. These three examples indicate that the results from dose response studies using the ICRU rectum point will most probably give dose constraints valid for the specific treatment technique in question and will not be valid in general.

Several authors have investigated the correlation between the maximum rectum point dose and late complications [6,9,57,58,59], but only Sakata et al [9] and Noda et al [6] succeeded in showing a correlation. Except for the study by Noda et al, the determination of dose levels to the maximum point was either based upon x-ray imaging or by measurements in the rectum. Both of these methods will be inaccurate since several authors have shown that maximum rectum dose obtained by using x-ray imaging underestimates the dose compared to using CT [61,62,63] and since it is difficult to guarantee that measurements give the true maximal dose.

9.2. Predictive factors for late complications using 3D-based brachytherapy

A point dose is most probably inadequate to establish general constraints for OARs that receive a highly inhomogeneous dose distribution. Dose-volume constraints and thus sectional imaging with 3D planning, are required [11,26]. Koom et al investigated the correlation between dose-volume parameters for the rectum and rectal mucosal changes observed by flexible sigmoidoscopy after combined EBRT and ICBT [64]. For 71 patients they scored their sigmoidoscopy findings by using a 0-5 scale according to grade of congested mucosa, teleangiectasia, ulceration, strictures and necrosis. They showed that patients with score ≥ 2 and score < 2 had significant different dose in the ICRU rectum point (71 $Gy_{\alpha/\beta=3}$ versus 66 $Gy_{\alpha/\beta=3}$, p = 0.02) as well as higher values for D_{2cc} (75 $Gy_{\alpha/\beta=3}$ versus 69 $Gy_{\alpha/\beta=3}$, p = 0.02), D_{1cc} (80 $Gy_{\alpha/\beta=3}$ versus 73 $Gy_{\alpha/\beta=3}$, p = 0.02) and $D_{0.1cc}$ (93 $Gy_{\alpha/\beta=3}$ versus 85 $Gy_{\alpha/\beta=3}$, p = 0.04) [64]. Georg et al investigated the predictive value of the same DVH parameters for rectum, sigmoid colon and bladder from 145 patients treated at the General Hospital of Vienna. They found that patients with D_{2cc} > 75 $Gy_{\alpha/\beta=3}$ for the rectum had significantly higher incidence of late complications compared to patients with D_{2cc} below this dose level (20 % versus 4 %) [65]. For sigmoid colon they also found significant differences in late

complication incidence for the same cut-off level, with 9 % when D_{2cc} was above 75 $Gy_{\alpha/\beta=3}$ and 1 % when D_{2cc} was equal to or below 75 $Gy_{\alpha/\beta=3}$[65]. They could not find any significant cut of level for the bladder.

The two studies from Koom et al [64] and Georg et al [65] support the assumption that small volumes irradiated to high doses in rectum and sigmoid colon are important for development of late toxicity after brachytherapy. They also support the recommendation that the minimum dose in the most irradiated volume of 0.1, 1, 2 and 5 cm^3 in these OARs have to be recorded and reported [26,48,61,62].

When late GI and GU effects after EBRT alone are assessed the dose distribution in the *whole* rectum and bladder is usually evaluated and not only the high dose area, as is traditionally done after combined EBRT and brachytherapy. The results from pelvic dose-volume studies are derived mostly from patients treated with EBRT for prostate cancer [66,67,68,69,70,71].

Emami et al suggested in 1991 that V70-V80 (the volume of the 70 to 80 Gy isodose) should be used as a dosimetric parameter to indicate the probability of late complications in rectum [66]. This means that the high dose area is supposed to have predictive value, in line with the observations from the gynaecological treatments mentioned above. However, recent publications suggest that the risk of rectal complication is a continuous function of dose and volume [68,69,70,71]. A retrospective analysis from MD Anderson Cancer Center showed a significant dose volume effect for V60, V70, V76 and V78 [68], while an Italian multicentre study showed that V50-V70 were predictive factors for late rectal complications [69]. Karlsdottir et al analysed late complications in 247 patients with cancer of the prostate and observed statistically significant correlation between V40-V43 and late GI complications (≥ Grade 2) [70]. They also observed that V71-V74 approached, but did not reach, statistically significant correlations. It is suggested that these observations could be explained by assuming that when the high-dose area is surrounded by extensive volumes receiving intermediate doses, the ability of this surrounding tissue to aid in the repair of higher dose areas is inhibited [70]. This may indicate that the intermediate dose regions of rectum should also be included in the dose response analyses after radiotherapy for cervical cancer.

Both Emami [66] et al and Marks et al [72] suggested that the frequency of bladder complication is not only related to the regions with high dose levels, but also to intermediate dose levels. However, these publications are based on limited available clinical data. Results from resent studies do diverge considerably. Karlsdottir et al do not find correlation between

any DVH-parameters and late bladder toxicity [70], while other suggest that the high dose areas are important [73,74] or that V30 and V82 correlate with late GU toxicity [75]. These divergent results, together with the results from Georg et al [65], show that further investigations are needed. To be able to investigate the predictive ability of the intermediate as well as the high dose regions, the whole dose distribution in the bladder should be included in the analyses and not only D_{2cc}, D_{1cc} and $D_{0.1cc}$ as suggested by Pötter et al [26].

In paper IV the relationship between the whole organ volume and dose to the organ wall is discussed for rectum and bladder. Figure 4 in this paper shows a scatter diagram of median dose to the organ wall versus the volume of the rectum (a) and bladder (b) for all the 69 CT examinations [paper IV]. In both plots a linear regression analysis was performed and a linear correlation coefficient (R) was calculated. The same calculations could be performed for each volume fraction and in Figure 10 the linear correlation coefficient is plotted as a function of the maximum dose to a volume fraction of the wall for rectum (a) and bladder (b).

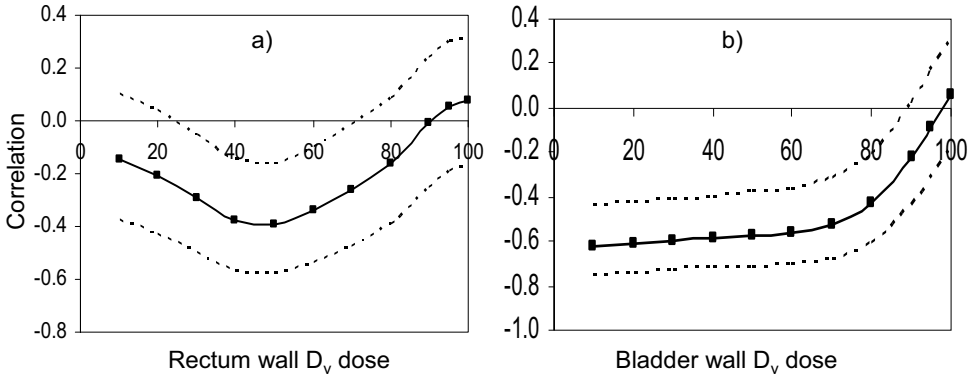

Figure 10. The linear correlation coefficient as a function of the maximum dose to a volume fraction of the wall for rectum (a) and bladder (b). $D_{v=50}$ is the median dose and $D_{v=95}$ is approximately D_{2cc} (see chapter 9.3). Dotted lines show 95 % confidence intervals.

Figure 10 shows that R is significantly different from zero for intermediate dose levels. The correlation is negative both for rectum and bladder. This means that a large organ volume will be associated with a lower median dose compared to a small organ volume. The correlation is rather strong for the bladder (R~ -0.6), while only a weak correlation is seen for the rectum (R~ -0.4). For the high dose regions (e.g. $D_{v=95} \sim D_{2cc}$), however, there is no significant correlation, i.e. the organ volume does not influence the high dose regions. This implies that for organs where intermediate dose levels are a strong predictor for toxicity, the organ should

be as large as possible. For organs where the high dose levels predict the toxicity the organ volume is not important. Data available at the time that paper IV was published indicated that the bladder showed features consistent with the first category, while rectum demonstrated to be of the latter. However, as discussed above, new data tend to modify these theories. Consequently, using a standardised bladder volume, as suggested in paper IV may not be that important.

Most of the publications discussed above include studies based on prostate patient cohorts receiving EBRT alone. In treatment of advanced cervical cancer a combination of EBRT + ICBT is always used. The dose distribution will therefore differ considerably. Is it adequate to apply data assessed from EBRT-alone studies on patients receiving combined treatment? In principle a specific dose level should give the same biological result irrespectively of treatment modality. However, since the dose distribution is very different between EBRT-alone treatment and combined treatment, it is important to keep in mind that underlying factors not related to the dose distribution could play an important role. The most optimal scenario will be to have dose-volume studies based on comparable dose distributions, but for the time being the number of such studies is limited.

9.3. Whole organ or organ wall?

Many publications analyse DVH for whole organs including filling, while others analyse DVH based on organ wall delineation, so called dose-wall-histogram (DWH). In the prostate cancer studies mentioned above, all the DVH and DWH parameters are relative, i.e. the y axis in the histogram is given as a percentage of the total organ volume instead of an absolute volume. If a histogram with y axis expressed as absolute volume is based on delineation of the whole organ including filling, the volume will also include dose statistics for the filling, which will hamper the analysis. In the GEC-ESTRO guidelines it is recommended to delineate the whole organ including filling *and* to use absolute volumes [26]. This is justified by the fact that it is recommended to record and report only minimum dose in the most irradiated 0.1, 1 and 2 cm^3 in the OARs. These DVH parameters will be the same for the organ and the organ wall [27,28]. However, if the whole dose distribution should be analysed for cervical patients, the organ wall has to be delineated if the recommendation of absolute volumes should be followed. In paper IV and V both the rectum and bladder wall, as well as the whole organs were delineated. The delineation of the inner contour of the organ is challenging and time consuming. However, a method for generating the organ wall solely based on the external contour does exist [76,77] and could be helpful in the organ wall delineation process.

In paper IV and V the maximum dose to 95 % of the total bladder and rectum wall is considered as the clinically relevant maximum dose to the OARs, denoted $D_{v=95}$. This is a somewhat different terminology compared to the GEC-ESTRO recommendations where the minimum dose to the most irradiated 0.1, 1 and 2 cm^3 volumes are considered [26]. However, $D_{v=95}$ is the same as the minimum dose to the most irradiated 5 % of the organ. According to paper IV, the average wall volume for the all the patients included in the analyses was 48.4 cm^3 and 60.1 cm^3 for the rectum and bladder, respectively. Thus, $D_{v=95}$ corresponds in average to $D_{2.4cc}$ for the rectum and D_{3cc} for the bladder. These rather small deviations will most probably not influence the conclusions drawn in paper IV.

9.4. Parameters in the LKB model

The intention of using NTCP models is to quantify the risk of developing late complications for a specific treatment through mathematical expressions. Since OARs usually receive an inhomogeneous dose distribution, most models take into account the whole dose-volume-histogram of the normal tissue in question. To be able to use the NTCP models clinically, the models should be fitted to clinical data to determine the various parameters. Moreover, it is important to verify the models by comparing calculated NTCP values with clinical incidence. In paper V the LKB model was fitted to data given by Boersma et al [78] and Marks et al [72] and n (describing the volume dependence) was estimated to 0.06 and 0.13 for the rectum and bladder, respectively, while $TD_{50}(1)$ was estimated to be 80 Gy and 62 Gy. An average NTCP was calculated for the rectum (19.7 %) and bladder (61.9 %) for 14 patients and these values were compared to the clinical incidence of late rectum (13 %) and bladder (14 %) complications for patients that had received the same type of treatment. The significant difference between the calculated and the clinical rectal incidence could, at least partly, be explained by the uncertainties in the parameters of the model. However, in the analysis of the impact of parameter uncertainties for the bladder, a $TD_{50}(1)$ of 67 Gy resulted in a calculated NTCP of 39.4 %, i.e. still considerably higher than the clinical incidence of 14%. As pointed out in paper V, available literature on the LKB model fitted to dose-volume-response data for the bladder was sparse at the time of this publication. In 2007 Cheung et al fitted several NTCP models to their data, including the LKB model using equation 10 [74]. In contrast to previous publications they estimated n = 0.01, m = 0.022 and $TD_{50}(1)$ = 77.6 Gy for the bladder [74]. The very low n could indicate that the bladder is more sensitive to small volumes of high doses and that the hotspots might be more important for developing GU toxicity than anticipated in paper IV and V. Cheung et al also showed that the “hottest volume

model" was best fitted with threshold dose of 78 Gy and optimal "absolute hottest" volume was 5.3 cc [74]. It is important to notice that these data are fitted to numbers for all grades of bladder toxicity and are based on dose-volume information from one single planning CT. Nevertheless, the conclusion supports the assumptions expressed in the GEC-ESTRO recommendations that small volumes irradiated to high dose seems to be of major interests when predicting late effects in the bladder [26].

In the last few years several authors have fitted the LKB model to clinical data of late rectal complications [79,80,81]. Soehn et al estimated n = 0.08 and $TD_{50}(1)$ = 78.4 Gy [81] and this is in good agreement with our results in paper V. Both Rancati and Peeters analysed data from large patient cohorts (547 and 648 patients, respectively) and fitted the LKB model to different endpoints. In the Italian multicentre study the n was estimated to 0.23 and $TD_{50}(1)$ = 81.9 Gy for rectal bleeding higher or equal to grade 2, while the same parameters were found to be 0.06 and 78.6 Gy when they analysed the severe bleeders only [79]. They concluded that dose-volume-response of rectum seems to be dependent of both the endpoint in question and the severity of the complication. This is supported by Peeters et al who found n = 0.13/$TD_{50}(1)$ = 80.7 Gy for rectum bleeding, n = 0.49/$TD_{50}(1)$ = 83.2 Gy stool frequency and n = 9.08/$TD_{50}(1)$ = 104.4 Gy for incontinence [80].

9.5. Uncertainties in 3D treatment planning

The ability of finding predictive dose related factors for late complication is limited by uncertainties in the dose distribution and dose-volume-histogram, i.e. uncertainties in the 3D treatment planning procedure. These uncertainties are linked to dose calculation, applicator reconstruction and delineation process. In paper II uncertainties of the reconstruction process for the ring applicator using CT imaging were evaluated. The calculations showed that the standard deviation of dose around the applicator did not exceed 3.7 % for any of the reconstruction methods. In the discussion it was pointed out that these figures are valid for CT-based reconstruction only, while MR-based reconstruction most probably will be encumbered with larger uncertainties. This is linked to the problem of visualising the track of the source in a T2 weighted MR image. At the moment no MR source track markers are commercially available. However, several groups have tested copper sulphate ($CuSo_4$) or gadodiamide as MR markers and developed in house solutions [82,83,84]. Haack et al investigated MR-based applicator reconstruction uncertainties using a $CuSo_4$-filled plastic tube and a stereotactic phantom. They performed an analysis of the geometrical uncertainties, in contrast to our study, and found a deviation of less that 1.1 mm between MR and CT

imaging [82]. They also performed an inter-observer study where 69 applicators were re-reconstructed. For the plastic applicator the largest deviation between the two reconstructions was found in the longitudinal direction with a mean value of -0.5 mm (1SD = 1.4 mm) [82]. In paper IV a re-reconstruction analysis was performed. This analysis was performed by only one observer and is of course not an inter-observer analysis. Nevertheless, this analysis will give an indication of the uncertainties of reconstructing the applicator several times and could therefore be compared with an inter-observer study. In the re-reconstruction analysis a relative standard deviation of 5.6 % was found for $D_{v=95}$ (~D_{2cc}) for the rectum [paper IV]. By using the results from paper III (figure 2) this deviation could be explained by an applicator shift of approximately 1-1.5 mm in the longitudinal direction, in well accordance with the results from Haack et al.

Kubicky et al estimated minimum and maximum error due to applicator reconstruction to be 1.625 mm and 3.25 mm, respectively [84]. Moreover, from a previous analysis [85] they estimated the average dose uncertainty to be 1-2 % [84]. Shifting our ring applicator set by 3.25 mm along the tandem applicator using the same source configuration as in paper II results in approximately 3 % dose change in point P1 (close to point A), point P2 (close to point A) and point P5 (bladder). In point P3, point P4 (approximately 5 mm from the surface of the ring, left and right) and point P6 (rectum) a 3.25 mm applicator shift results in approximately 6 % dose change. These dose uncertainties are considerably higher than the estimated value by Kubicky et al of 1-2 %. These estimations, however, are based on random shift of 16-18 applicators in an interstitial prostate implant [85]. A shift of 3.25 mm of two intracavitary applicators will most probably have larger dosimetric consequences, especially when the dose distribution is conformal to a delineated target volume.

The delineation process is also an important part of the treatment planning procedure. Several observers may interpret image information differently resulting in an inter-observer variation. Saarnak et al investigated the consequences of inter-observer variation in delineation of bladder and rectum contours on DVH-parameters [86]. Three experienced persons delineated rectum and bladder in CT images from ten patients treated with intracavitary brachytherapy. They found that the variation (1SD) in the total volume for all patients were 33 % and 10 % for the rectum and bladder, respectively. For the rectum these uncertainties were followed by a variation (1SD) of 11 % for both D_{2cc} and D_{5cc}, while the corresponding figures for the bladder was 10 % and 8 % for D_{2cc} and D_{5cc}, respectively [86]. Saarnak et al used CT imaging. However, in the GEC-ESTRO recommendation it is strongly advised to use MR-based treatment planning [11,26]. Viswanathan et al showed that

delineation of rectum and bladder corresponded well between CT and MR imaging [87]. Thus, most probably the results from Saarnak et al will also be valid for MR-based treatment planning. Publications about inter-observer contouring in 3D MR-based brachytherapy for cervical cancer are few. Nulens et al compared delineated contours on six patients performed by three observers. The average standard deviations for the six patients were 50 %, 21 % and 15 % for the GTV, HR-CTV and IR-CTV, respectively [88]. These large deviations were, however, not followed by a corresponding deviation in the D90 and D100. For the HR-CTV and IR-CTV the average standard deviation was less than 5 %, while the corresponding figure was 11 % for the GTV [88].

From the above mentioned studies it is reasonable to conclude that uncertainties in the delineation process have the highest impact on the total uncertainty budget in 3D-based treatment planning in gynaecological brachytherapy.

9.6. Multiple fractions and adding ICBT and EBRT

Even if the uncertainties described above could be important, the major challenge in calculating the accumulated dose distribution and DVHs from a full treatment of ICBT and EBRT is to establish a method for taking into account the contribution from each fraction. The dose gradient in a brachytherapy implant is usually steep. Thus, small changes in the positions of a structure or in the position of the applicator could lead to rather large changes in DVH of the structure. Usually only one fraction is delivered per application, i.e. the applicator is inserted prior to each dose delivery. The bladder, the rectum and the sigmoid colon could potentially change position relative to the applicator and consequently the dose distribution to these organs may change. Hoskin et al and Dattta et al investigated variation of applicator position during multiple gynaecological HDR ICBT insertions and the impact of the dose to the ICRU reference points [89,2]. Both of these studies are based on x-ray imaging and using this image modality it is not possible to produce dose-volume-histograms, as described in chapter 9.1. In paper IV the inter-fraction variations in DVH parameters for the rectum and bladder were investigated for 13 treatment series of ICBT based on CT imaging. The mean standard variation the DVH parameters varied between 15 % and 19.9 %. If only one single CT examination was used to estimate the total dose, the SD of the relative deviation was 13 % and 19 % for the rectum and bladder, respectively. If four scans were provided SDs of 7 % and 4 % were found [paper IV]. Kirisits et al investigated the same topic using MR-based treatment planning for 14 patients [90]. They calculated the total dose distribution based on individual MR treatment plans for each insertion (multiple plans) and compared the results

with the total dose distribution estimated from the MR examination of the first insertion only (single plan). The accumulated D_{2cc} and D_{1cc} for the rectum, bladder and sigmoid colon were significantly higher for single plan compared to multiple plans. The mean increase was 9 %, 22 % and 28 % for the bladder, rectum and sigmoid colon respectively [90], which is in the same order of magnitude as the results in paper IV. Moreover Kirisits et al found that when using multiple plans 3 patients did exceed the bladder constraints of $90_{\alpha/\beta=3}$ Gy (EQD_2), while using one single plan 5, 1 and 5 patients exceed the bladder, rectum and sigmoid colon constraints respectively ($EQD_2 = 75_{\alpha/\beta=3}$ Gy for the rectum and sigmoid colon) [90]. This means that there is a risk of estimating too high doses to the OARs if only one examination is used for a fractionated brachytherapy schedule. Hence, a potential decision on reducing the dose will then be based on an incorrect foundation.

Many publications evaluate total dose distribution and DVHs from treatments where ICBT and EBRT are combined [paper III, IV and V,27,45,48,64,65,84,88,90]. Even if several of these evaluations are based upon multiple CT or MR examinations of the ICBT implant, a major problem is how to combine dose distributions in a structure from different image acquisitions. Most probably the ideal method is to match the 3D structures by a warping technique and to obtain a voxel to voxel transformation between 3D images. This is, however, a complex and tedious procedure that requires specially developed software. A simpler and more applicable approach is to sum the DVHs directly as have been performed in paper III, IV and V. The method of summing doses given to the same volume is based on the assumption that there is a similar dose gradient over the organ in each fraction and that it is the same 2 cm^3 volume that receives the highest dose each time. This assumption is most probably not valid in general and estimated values for the D_{2cc}, D_{1cc}, D_{1cc} and $D_{v=95}$ D_{1cc} could be too high. Kirisits et al refer to this method as “worst case assumption” [48]. In organs with high maximum dose dependence (low n) this may overestimate the calculated NTCP.

10. Conclusions

The overall aim of this thesis was to address important aspects regarding the introduction of 3D image based HDR brachytherapy for cervical cancer patients, with special focus on severe late complications. The work has revealed that:

- Neither the dose to point A nor the dose to ICRU reference points could predict severe late effects in cervical cancer patients treated with combination of EBRT and ICBT.
- There are indications that 20 Gy may be an upper limit for the dose to be delivered each week to avoid severe rectum and bladder complications for a total dose above a certain level.
- The consequence of ring applicator reconstruction uncertainties on the calculated dose to points around the applicator is less that 3.7 % for any reconstruction method. This is considerably smaller than the uncertainties caused by inaccuracies in the delineation process.
- The impact of applicator uncertainties on D_{2cc} for rectum and bladder was most pronounced in the anterior-posterior direction with a mean of approximately 5 % change per mm of applicator displacement.
- Even if inter fraction variations of bladder and rectum volume may be large it is not followed by a corresponding inter fraction variation for DVH parameters. It seems like there is a negative correlation between organ volume and intermediate dose levels, while the high dose levels do not correlate with the organ volume.
- The mean NTCP of rectum calculated for 14 patients was comparable to the clinical complication frequency, while the mean NTCP of the bladder was too high. The latter was probably explained by the conservative tolerance data from which the NTCP model parameters were derived.

11. Further perspectives

A wide implementation of 3D image based brachytherapy relies on evidence based assessments of clinical impact. There are already indications that 3D image based brachytherapy improves local control and reduces morbidity for patients with locally advanced cervix cancer [91]. Verification of these promising results should be performed in a prospective clinical trial with thorough assessment of response and morbidity for this patient group. Such recording in combination with recording of 3D dose distributions in relation to clinical structures, will allow assessing dose-volume response relationship and radiobiological modelling. The dose distribution in the whole bladder and rectum should be evaluated to find potential predictive factors other than the "traditional" high dose areas. This implies that the organ wall should be delineated in order to be able to use absolute dose-volume-histograms. The accumulated dose per week to OAR should also be recorded to establish possible upper dose limits to avoid severe late toxicity. The development of new methods for 3D assessment of treatment related morbidity could allow for direct spatial comparison between dose and effect and can lead to deeper understanding of the mechanisms involved in the development of late effects following radiotherapy.

12. References

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